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Synthesis of A_3B-phthalocyanine derivatives bearing N-heterocycles as potential cationic photodynamic agents

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Abstract

Unsymmetrically substituted A_3B-phthalocyanine derivatives bearing annulated 6-membered N-heterocycles, pyridine and pyrazine rings, have been synthesized by ring expansion reaction of subphthalocyanines. The geometrically constrained subphthalocyanines (A_3) were reacted with 1,2-phthalonitrile derivatives (B), in presence of 8-diazabicyclo[5.4.0]undec-7-ene (DBU), to form the A_3B-phthalocyanine. The reactions were carried out in DMSO/1-chloronaphthalene at 130-140 °C for 15 h. This approach produces selectively A_3B-phthalocyanines with high yields (75-90%) and it requires simple purification procedure since there are not byproducts. The spectroscopic properties of the A_3B-phthalocyanines were compared with its homologous non-substituted Zn(II)phthalocyanine. In these compounds, annulated 6-membered N-heterocycles are precursors of cationic groups by methylation and therefore they represent interesting agents with potential applications in photodynamic inactivation of microorganisms.

Introduction

Unsubstituted phthalocyanines and many of the substituted ones are highly symmetrical compounds. A great number of unique properties arise from their electronic delocalization, which makes these compounds valuable in different application fields. However, the intrinsic symmetry of the molecule sometimes represents a limitation for many purposes. Thus, the possibility of designing and synthesizing unsymmetrical compounds with substituents located at specific position allows enhancing the application of phthalocyanines [1].

In recent years, cationic phthalocyanines have shown important applications as sensitizers to photoinduce direct inactivation of multidrug resistant microorganisms [2,3]. The positive charge on the photosensitizer molecule appears to promote a tight electrostatic interaction with negatively charged sites at the outer surface of the bacterial cells. This association increases the efficiency of the photoinactivation processes [4]. Also, the combination of hydrophobic and hydrophilic substituents in the sensitizer structure results in an intramolecular polarity axis, which can facilitate membrane penetration and produces a better accumulation in subcellular compartments, enhancing the effective photosensitization. The design of amphiphilic sensitizer architecture requires the formation of phthalocyanines bearing one different (B) and three identical (A) isoindole subunits (A_3B type). Different strategies have been employed for the preparation of these low-symmetry derivatives. Statistical condensation is the most widely used strategy to prepare A_3B-phthalocyanines. This non-selective method is based on the reaction of two differently substituted phthalonitriles and it affords a mixture of six compounds. This way demands the use of chromatographic techniques for the isolation of the desired macrocycle. A selective approach to prepare A_3B-phthalocyanines involves ring expansion reaction of subphthalocyanines [5]. Good yields are obtained when the phthalocyanine is treated with phthalonitriles in the presence of a strong base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and a metal salt.

In previous studies, we have investigated the photodynamic activity of phthalocyanines derivatives in different biomimetic media and *in vitro* on human carcinoma cells and microorganisms [6-8]. In particular, the photoinactivation capacity of a cationic Zn(II) tetramethyltetrapyridinoporphyrazinium salt was compared with that of a non-charged Zn(II) tetrapyridinoporphyrazine, both *in vitro* using human red blood (HRB) cells and a typical Gram-negative bacterium *Escherichia coli*. Both phthalocyanines produce similar photohemolysis of HRB cells, however, only the cationic phthalocyanine produces significant photoinactivation of Gram-negative bacteria [7]. In this way, one of the mainly problems that affect the sensitizing ability of the phthalocyanines is the aggregation tendency due to the large π conjugate systems [9]. The aggregates present an efficient nonradiative energy relaxation pathway, diminishing the triplet-state population and the $O_2(^1\Delta_g)$ quantum yield. Therefore, the formation of aggregation precludes the photodynamic activity.

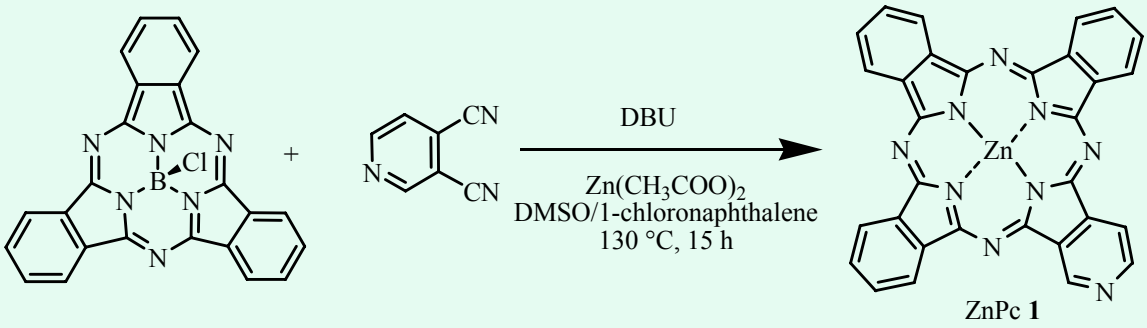
Taking into account these considerations, in this paper we report the synthesis of unsymmetrically substituted A_3B-phthalocyanine derivatives bearing annulated 6-membered N-heterocycles, pyridine and pyrazine rings. Thus, subphthalocyanines (A_3) were reacted with 1,2-phthalonitrile derivatives (B) in presence of DBU and Zn(II) acetate to form the A_3B-phthalocyanine. This approach produces selectively A_3B-phthalocyanines with different substitution

pattern, which can be interesting phototherapeutic agent with potential applications in photodynamic inactivation of microorganisms.

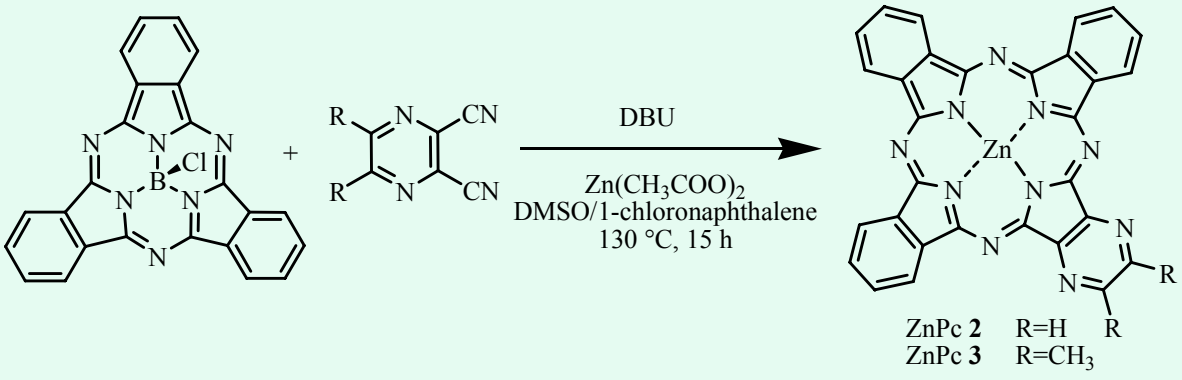
Synthesis of A_3B-phthalocyanines

The subphthalocyanine complexes were used as starting materials for the formation of unsymmetrically substituted phthalocyanines by ring expansion employing substituted phthalonitriles. This method has gained popularity over using statistical condensation of two differently substituted phthalonitriles derivatives because the later results in a complex mixture of products. The A_3B-phthalocyanine derivatives were synthesized by ring expanding of subphthalocyanine with 1,2-phthalonitrile derivatives. First, subphthalocyanine (SubPc) was reacted with 3,4-pyridinedicarbonitrile to obtain ZnPc **1** with 90% yield (Scheme 1). The ring of SubPc was also expanded with pyrazine-2,3-dicarbonitrile and 5,6-dimethylpyrazine-2,3-dicarbonitrile. These reactions produce ZnPc **2** (90%) and ZnPc **3** (89%), respectively (Scheme 2, Table 1).

The structure of ZnPc **1** is precursors of an unsymmetric A_3B monocationic phthalonitrile, while ZnPc **2** and **3** can be used to produce dicationic phthalocyanines by methylation of annulated 6-membered N-heterocycles [7].

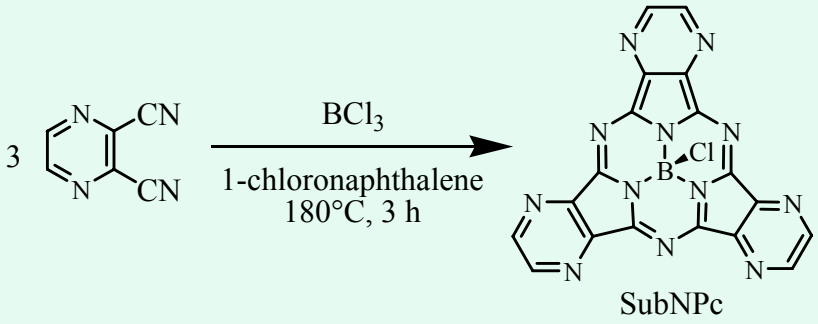


Scheme 1. Synthesis of A_3B-phthalocyanine **1**

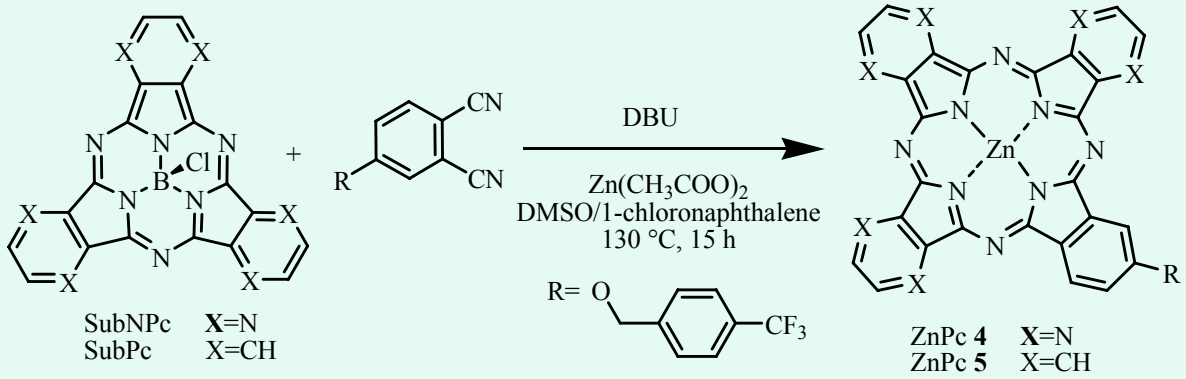


Scheme 2. Synthesis of A_3B-phthalocyanines **2** and **3**

On the other hand, subphthalocyanine ring expansion was evaluated using 4-(4'-trifluoromethylbezyloxy)phthalonitrile (Scheme 4). The influence of the trifluoromethyl group in biologically active molecules is often associated with the increased lipophilicity that this substituent imparts [10]. This highly lipophilic group increases the amphiphilic character of the structure [11,12]. First, a new subphthalocyanine containing three annulated 6-membered with two N-heterocycles was synthesized (Scheme 3). The boron trichloride-induced cyclotrimerization of pyrazine-2,3-dicarbonitrile was performed in 1-chloronaphthalene. After that, the mixture reaction was heated at 180 °C for 3 h and then cooled to room temperature. The product was precipitated with hexane and re-crystallized to obtain SubNPc with 25% yield (Table 1). The expansion of SubNPc produces ZnPc **4** with 77% yield. This structure can be used to obtain a hexacationic phthalocyanine bearing a chain with a high lipophilic trifluoromethyl group. In addition, SubPc was also expanded with 4-(4'-trifluoromethylbezyloxy)phthalonitrile to give ZnPc **5** (88%).



Scheme 3. Synthesis of subphthalocyanines SubNPc



Scheme 4. Synthesis of A_3B-phthalocyanines **4** and **5**

General procedure. A solution of phthalonitrile derivative (0.14 mmol) and DBU (0.066 mmol) in 4 mL of DMSO/1-chloronaphthalene (5:1) was heated to 130 °C. Then, a suspension of the

appropriate subphthalocyanine (0.10 mmol) and zinc(II) acetate dihydrate (22 mg, 0.10 mmol) in 2 mL of DMSO/1-chloronaphthalene (5:1) was added drop-wise to the heated mixture over a period of 1 h. The reaction was kept at 130-140 °C for 15 h. The reaction mixture was cooled to room temperature and precipitated with 50 mL of water. The product was separated by centrifugation. The solid was re-suspended in cyclohexane and phthalocyanine isolated by precipitation.

Table 1. Synthesis of A_3B-phthalocianines by ring expansion reaction of subphthalocyanines.

ZnPcs	Yield (%)	δ (ppm) DMSO-d_6	Formula	MS [m/z]
1	90	8.26 (s, 6H), 9.20-9.70 (m, 8H), 11.0 (s, 1H)	$C_{31}H_{15}N_9Zn$	577
2	90	8.22 (s, 6H), 8.80-9.40 (m, 8H)	$C_{30}H_{14}N_{10}Zn$	578
3	89	2.99 (s, 6H), 8.24 (s, 6H), 9.38 (s, 6H)	$C_{32}H_{18}N_{10}Zn$	606
4	77	4.5 (s, 2H), 7.3-8.1 (m, 7H), 9.6 (s, 6H)[a]	$C_{34}H_{15}F_3N_{14}OZn$	756
5	88	.5 (s, 2H), 7.3-8.1 (m, 7H), 8.29 (s, 6H), 9.46 (s, 6H)[b]	$C_{40}H_{21}F_3N_8OZn$	750
SubNPc	25	8.93 (s, 6H)	$C_{18}H_6BClN_{12}$	436

^{19}FNMR δ (ppm) [a] 60.97 (s, -CF_3), [b] 60.95 (s, -CF_3)

Spectroscopic studies

The absorption spectra of ZnPcs **4** and **5** in N,N-dimethylformamide (DMF) are gathered in Figure 1A. The spectra show the typical Soret and *Q*-bands, characteristic of zinc(II) phthalocyanines (ZnPc) [13]. The spectroscopic properties in DMF are summarized in Table 2. A sharp absorption band was obtained in this organic solvent indicating that there is not aggregation of these ZnPcs in the systems. The *Q*-band wavelength of A_3B-phthalocianies with only one ring different of ZnPc (ZnPcs **1**, **2**, **3** and **5**) is very similar to that found for unsubstituted ZnPc. However, when the macrocycle contains three annulated 6-membered N-heterocycles of pyrazine derivative, the Q-band presents a hipsocromic shift by ~30 nm when compared with that of ZnPc (Table 2).

The steady-state fluorescence emission spectra of ZnPcs **4** and **5** were performed in DMF (Figure 1B). Similar behavior was found for the other ZnPcs **1**, **2** and **3**. The spectra show two bands in the red spectral region, which are characteristic for similar Zn(II) phthalocyanines [13]. By comparison with ZnPc as a reference, the values of fluorescence quantum yields (ϕ_F) were obtained in DMF. Values of ϕ_F are shown in Table 2. A small Stokes shift (~8 nm) was observed indicating that the spectroscopic energy is nearly identical to the relaxed energy of the singlet state. Taking in account the energy of the 0-0 electronic transitions, the energy levels of the singlet excited stated (E_s) were calculated (Table 2). These results are in agreement with those previously reported for similar phthalocyanines in different media [14].

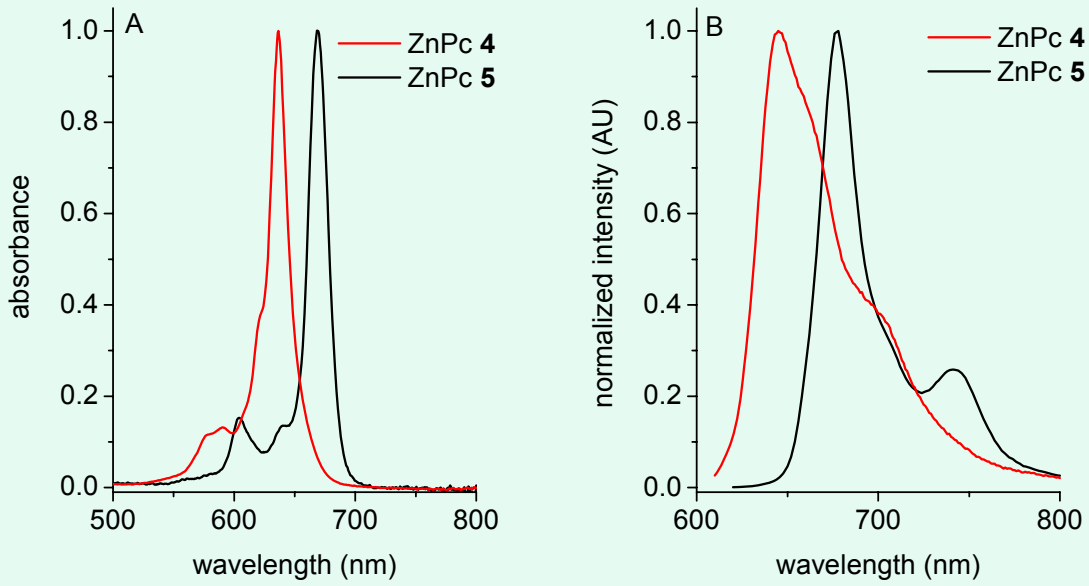


Figure 1. (A) Absorption and (B) fluorescence emission spectra of ZnPc **1** (λ_{exc}=600 nm) and ZnPc **2** (λ_{exc}=610 nm) in N,N-dimethylformamide (DMF).

Table 2. Spectroscopic characteristics of A_3B-phthalocyanines in DMF.

Phthalocyanine	λ_{max}^{abs} (nm)[a]	λ_{max}^{em} (nm)[b]	ϕ_F	E_s (eV)[d]
1	670	679	0.19±0.01	1.85±0.03
2	668	674	0.21±0.01	1.84±0.04
3	668	674	0.15±0.01	1.84±0.02

4	636	645	0.08±0.01	1.75±0.02
5	668	673	0.29±0.01	1.83±0.03
ZnPc	669	675	0.28±0.01[c]	1.84±0.03

[a]Q-band, [b]λ_{exc}=610 nm, [c]ϕ_F=0.28 ref. [8], [d]singlet excited stated energy.

Conclusions

In summary, novel unsymmetrically substituted A_3B-phthalocyanine derivatives were synthesized by ring expansion reaction of subphthalocyanines. These macrocycles presents different pattern of substitution by annulated 6-membered N-heterocycles, pyridine and pyrazine rings. To obtain A_3B-phthalocyanine, the geometrically constrained subphthalocyanines (A_3) were reacted with 1,2-phthalonitrile derivatives (B), in presence of 8-diazabicyclo[5.4.0]undec-7-ene (DBU) and Zn(II) acetate. The reactions were carried out in DMSO/1-chloronaphthalene at 130-140 °C for 15 h. This approach produces selectively A_3B-phthalocyanines, which are easily purified because this procedure does not produce significant byproducts. Thus, unsymmetric type A_3B macrocycles are obtained with high yields (75-90%). The annulated 6-membered N-heterocycles present in these compounds are precursors of cationic groups by methylation. Positively charges in the macrocycle periphery in combination with high lipophilic group can be used to obtain amphiphilic photosensitizers, which represent interesting agents with potential applications in photodynamic inactivation of microorganisms.

Acknowledgements

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